REMARKS

Claims 1-34 are pending in this application. Claims 10-33 have been withdrawn from consideration by the Examiner in view of the restriction and election requirements, which have been made final. However, the withdrawn claims have not been cancelled, since as the Examiner pointed out in the last two paragraphs of item 1 of the Detailed Action, rejoinder may be possible. Claims 1 and 34 are the independent claims among the claims that have not been withdrawn. Claims 15, 18 and 25 are independent claims among the withdrawn claims.\

Claims 1 and 3-6 have been amended and new claim 34, which reads on the elected group of claims, has been added. The amended and newly added claims do not include new matter, as indicated below. The withdrawn claims, upon an indication of rejoinder, will be amended at least to correct spelling of various terms into an American English form, such as "hybridize" and its variants in place of "hybridise" and its variants.

Claim 1 has been amended without being narrowed to recite that the set of oligonucleotide probes is capable of detecting at least one target polynucleotide selected from the recited plurality of different target polynucleotides. This amendment is supported at least in paragraph **[0083]** of the originally filed specification. Claim 1 has also been amended to recite that at least one target polynucleotide comprises at least two target sequences shared with one or more other target polynucleotides. This amendment is supported at least in paragraph **[0084]**, Example 1 (*i.e.,* paragraphs **[0137]-[0149]**) and Figures 2b and 5-8 of the application as originally filed.

Claims 1 and 3-6 have been amended to correct spelling to the American English format, as requested by the Examiner. None of the amendments has been made to overcome any rejection based on any ground affecting patentability. Rather, the amendments have been made to more particularly point out and distinctly claim the subject matter that Applicants regard as their invention.

Newly added claim 34 is essentially similar to amended claim 1 with the exception that it recites at least two target polynucleotides each comprising at least two target sequences, at least one of which is shared with one or more other target polynucleotides. This amendment finds support in the specification as originally filed at least in paragraph **[0083]**.

For the foregoing reasons, Applicants respectfully assert that the amendments and additions made herein are fully supported by the specification and do not include new matter. Entry of the amendments are respectfully solicited.

Rejection of Claims under 35 U.S.C. § 102

The Examiner has rejected claims 1-4 and 6-8 under 35 U.S.C. § 102(e) as allegedly anticipated by Austin *et al.* (U.S. Patent No. 6,132,965). The Examiner alleges that Austin *et al.* teach a set of oligonucleotide probes comprising a plurality of different predefined combinations of probes, each providing specificity of detection of a different target polynucleotide and draws attention to column 11, lines 15-30 and column 12, lines 11-40 of this reference. For convenience, these passages are reproduced below.

Column 11, lines 15-30

> The invention provides a composition for diagnosing a homocysteine-related pathological condition, comprising a polynucleotide probe comprising at least 25 nucleotide which are substantially identical to a dhc-1 gene sequence, typically at least 35 nucleotide which are substantially identical to dhc-1. In an aspect, the polynucleotide probe is labeled. In an aspect, the polynucleotide probe is immobilized, such as on a solid substrate or DNA probe array. In an aspect, the dhc-1 polynucleotide is used as a primer for PCR amplification, often in conjunction with a second (reverse) primer which may be a dhc-1 polynucleotide, an oligo(dT) primer, a randomer or mixture of randomers or nested set of promiscuous primers, or the like; however, some variations may employ spontaneous self-priming via hairpin loop formation in the absence of a second primer.

Column 12, lines 11-40

> In one aspect, the invention provides a polynucleotide (e.g., as a primer or probe) which specifically hybridizes to a predetermined homocysteine-regulated mRNA, wherein the polynucleotide is affixed to a solid substrate, typically wherein the solid substrate has a plurality of polynucleotide species affixed thereto, in a spatially defined array whereby each cell typically contains a single polynucleotide species, with the array often comprising in excess of 1000 distinct polynucleotide species. The probe polynucleotide is typically affixed by covalent linkage to the solid substrate. The solid substrate constitutes an array of polynucleotide probes and/or primers, wherein at least one member of the array is a probe polynucleotide for a predetermined homocysteine-regulated mRNA. Generally, the solid substrate will be less than 10 cm^3 and comprise at least 1024 positionally distinct polynucleotide species, at least one of which is a probe polynucleotide which binds to a predetermined homocysteine-regulated mRNA. Such polynucleotides arrays on solid substrates (e.g., a polysilicon wafer) can be used for genotype determination, disease detection and diagnosis, therapeutic efficacy monitoring, forensic identification, or for sequencing (e.g., of a pool containing unknown polynucleotides; for sequencing a mammalian genome or cDNA library), or other like uses.

> The invention provides a diagnostic kit for detecting a pathological condition, such as atherosclerosis and hyperhomocysteinemia, wherein the kit contains at least one polynucleotide predetermined to hybridize to a homocysteine-regulated mRNA or to prime amplification of a homocysteine-regulated mRNA.

However, Applicants strongly disagree with the Examiner's allegations. In broad terms, Austin *et al.* describe (1) a method for selectively enriching certain mRNA species that are produced in response to an abnormal physiological state, (2) a method for selectively amplifying cDNA species that are copies of such mRNAs and (3) a method for using such cDNA species, or probes developed from them, for diagnosing the abnormal state (*e.g.*, homocysteinemia).

Specifically, at columns 8-13, in the section entitled "Polynucleotides induced or repressed by homocysteine," Austin *et al.* describe polynucleotide species (mRNAs, ESTs, cDNA species and probes as well as primers) that have been identified by methods described in other parts of the patent. In the same section, Austin *et al.* describe various uses of those polynucleotide species, including their use for diagnosing an abnormal physiological state (*e.g.*, homocysteinemia).

The present application's claims are directed to a set of oligonucleotide probes for detecting a plurality of different target polynucleotides, wherein a respective target polynucleotide corresponds to a single polynucleotide or a group of related polynucleotides. The set includes a collection of different promiscuous probes, wherein a respective promiscuous probe is capable of hybridizing to a target sequence shared between at least two of the target polynucleotides and wherein at least one target polynucleotide (for convenience, this polynucleotide will be referred to as "the promiscuous probe-only detectable target polynucleotide") comprises at least two target sequences shared between other target polynucleotides. A predefined combination of promiscuous probes is capable of hybridizing to those target sequences, which provides specificity of detection of the promiscuous probe-only detectable target polynucleotide.

The passage delineated by lines 15-30 of column 11 of Austin *et al.* appears merely to relate to the use of an allele-specific primer with one or more randomer or promiscuous primers for the amplification of a specific allele. In column 11, lines 15 to 30, Austin *et al.* describe the use of a polynucleotide probe or primer "for diagnosing a homocysteine-related pathological condition." The probe or primer is specific for the dhc-1 gene and was derived from that gene sequence. Austin *et al.* state that the probe could be used as a primer in conjunction with a second reverse primer. The following several possible reverse primers are listed: "a dhc-1

polynucleotide, an oligo(dT) primer, a randomer or mixture of randomers or nested set of promiscuous primers, or the like." Clearly, the purpose of using the dhc-1 specific primer with a second reverse primer is to detect the dhc-1 mRNA or cDNA derived from that mRNA. This is clear from the stated purpose at lines 15 and 16, namely "diagnosing a homocysteine-related pathological condition" and from the stated purpose in the previous paragraph in column 11 at lines 6 to 14, namely "to determine if a predetermined pathognomonic concentration of dhc-1 polypeptide or its encoding mRNA is present in a biological sample from a human patient; if the assay indicates the presence of dhc-1 polypeptide or its encoding mRNA outside of the normal range (*e.g.*, outside the predetermined pathognomonic concentration range), the patient is diagnosed as having a disease condition or predisposition to developing premature atherosclerosis." This purpose is also described in the section entitled "Summary of the Invention" at column 5, lines 36 to 48.

Thus, the purpose of the method described by Austin *et al.* at column 11, lines 15 to 30, is not to identify any more than one target species, *i.e.*, the dhc-1 mRNA or cDNA. If the purpose is to identify other target species such as mRNA or cDNAs from other genes, they would only be identified using specific probes or primers as described in the section entitled "Summary of the Invention" at column 5, lines 36 to 48, where it states:

> The determination of the relative expression level of the homocysteine-regulated mRNA(s) is performed by a suitable diagnostic assay, which may include: (1) hybridization of an RNA sample of the sample to a polynucleotide probe of a predetermined sequence known to hybridize to said homocysteine-regulated mRNA, or (2) PCR, LCR, or other polynucleotide amplification method employing a primer or primer set of a predetermined sequence known to be capable of priming amplification of said homocysteine-regulated mRNA(s). Typically, the primer and probe sequences are obtained from a predetermined nucleotide sequence of an identified homocysteine-regulated mRNA or its cDNA.

It will be apparent, therefore, that, Austin *et al.* do not teach or suggest the use of a predefined combination of promiscuous probes for specific detection of a single target polynucleotide (*i.e.*, the promiscuous probe-only detectable target polynucleotide). Additionally, they fail to disclose promiscuous probes that are capable of binding to at least two target polynucleotides that are the subject of detection.

The Examiner also alleges that Austin *et al.* teach a set of oligonucleotide probes, comprising at least one probe that is capable of hybridizing to a pivot sequence, which divides

two or more polynucleotides into distinct groups. However, Applicants respectfully submit that the cited passage does not teach or suggest that feature.

Austin *et al.* make no comment on the possibility of a target polynucleotide containing sequences that are shared with other target polynucleotides.

From the foregoing, Applicants conclude that Austin *et al.* do not teach or suggest (1) the detection of a plurality of different polynucleotides, (2) the detection of a group of related polynucleotides, (3) promiscuous probes or promiscuous primers, (4) the properties of promiscuous probes or promiscuous primers, (5) a target polynucleotide that comprises at least two target sequences that are shared between other target polynucleotides, (6) a predefined combination of promiscuous probes, (7) the use of a predefined combination of promiscuous probes to provide specificity of detection of a single target polynucleotide and (8) a pivot sequence that divides two or more polynucleotides into distinct groups. Consequently, Austin *et al.* fail to disclose each and every one of the elements defined in the pending claims. For these reasons, Applicants respectfully urge the Examiner to reconsider and withdraw the rejection of claims 1-4 and 6-8 pursuant to 35 U.S.C. § 102(e).

Rejection of Claims Pursuant to 35 U.S.C. § 103

The Examiner rejects claim 5 as allegedly obvious under 35 U.S.C. 103(a) over Austin *et al.* in view of Pfahl (U.S. Patent No. 6,335,159). Claim 5 recites that the set of probes comprises at least one degenerate oligonucleotide probe which is capable of hybridizing to at least one redundant sequence. The Examiner asserts that even though Austin *et al* do not teach such a set of probes, Pfahl teaches this feature at column 5, lines 21-51. In particular, it is alleged that the passage at column 5, lines 34-49 states:

> In certain circumstances, one of skill in the art may find it desirable to prepare probes that are fairly long, and/or encompass regions of the amino acid sequence which would have a high degree of redundancy in corresponding nucleic acid sequences, particularly if this lengthy and/or redundant region is highly characteristic of the receptor protein.

On this basis, the Examiner asserts that an ordinary artisan would have combined and substituted a set of oligonucleotide probes, comprising at least one degenerate oligonucleotide probe which is capable of hybridizing to a redundant target sequence of Pfahl into the method of Austin *et al.* in order to improve the preparation of effective probes.

Applicants respectfully disagree with the Examiner's position because Pfahl is only concerned with detection of a single polynucleotide rather than a plurality of different target polynucleotides, and thus, is directed to solving a different problem than that addressed by the present invention. As such, Applicants conclude that a person of ordinary skill in the art would not be motivated by Pfahl to use a degenerate oligonucleotide probe in combination with an allele-specific probe or randomer taught by Austin *et al.* as a means of specifically detecting two or more target polynucleotides. At best, the combination of Austin *et al.* and Pfahl would motivate a skilled artisan to use a degenerate primer and an allele-specific primer in a PCR reaction to specifically detect a single target polynucleotide.

Claim 9 has also been rejected as allegedly obvious over Austin *et al.* in view of Krull *et al.* (U.S. Patent No. 6,503,711). The Examiner alleges that, although Austin *et al.* do not teach a set of oligonucleotide probes which are linked to a support *via* a spacer, Krull *et al.* supply that feature (referring to Example 2, column 27, lines 11-67). In particular, the Examiner asserts that Krull *et al.* disclose a soluble HEG linker to improve the ability of immobilized DNA strands to hybridize with complementary material in solution (column 27, lines 22-29).

Applicants concede that this feature was art-recognised at the filing date of the instant application. However, Austin *et al.*, even in combination with Krull *et al.*, fail to teach or reasonably suggest each and every one of the elements defined in the pending claims and consequently do not impact on the patentability of claim 9. At best, the combination of Austin *et al.* and Krull *et al.* would motivate a skilled person to use an allele-specific probe and a randomer (which would generally bind to any polynucleotide) for the detection of a single target polynucleotide, wherein the probe or randomer is linked to a support *via* a spacer.

For the foregoing reasons, Applicants respectfully urge the Examiner to reconsider and withdraw the rejection of claims 5 and 9 pursuant to 35 USC § 103(a).

Additional Claims Fees

The undersigned attorney first noticed when calculating the fees for the additional independent claim versus the fees previously paid that the multiple dependent claim 28, depending from two other claims, apparently was overlooked in computing the original filing fee on the basis of 37 original claims, rather than 39 original claims. It has not been determined whether the attorney's law firm's deposit account was charged for this underpayment, as originally authorized when the application was filed. Accordingly, to be certain to make up any

deficiency, payment is being submitted for a total of 40 claims and 4 independent claims, 3 more total claims than original paid for with one additional independent claim.

Summary

Applicants respectfully submit that every rejection of the pending claims has been overcome or is now inapplicable, and that each of claims 1-9 and 34 is in condition for allowance. Applicants respectfully urge the Examiner to reconsider and withdraw the rejections and allow each of these claims at the earliest possible date, and to rejoin the withdrawn claims in view of the patentability of the elected claims.

Respectfully submitted,

MARK JOHN GIBBS *et al.*

April 27, 2004 By: _____
(Date)

ALAN S. NADEL
Registration No. 27,363
AKIN GUMP STRAUSS HAUER & FELD LLP
One Commerce Square
2005 Market Street, Suite 2200
Philadelphia, PA 19103-7013
Telephone: 215-965-1200
Direct Dial: 215-965-1280
Facsimile: 215-965-1210
E-Mail: anadel@akingump.com

ASN:hg
Enclosures: Amendment Transmittal Sheet
Petition for Two-Month Extension of Time
Check in payment of the additional claims fee and the Extension fee